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FILING DATE: August 04, 2003

Certified by



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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

INVENTOR(S)					
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Simon		Côté		Beauport, Québec, Canada	
<input type="checkbox"/> Additional inventors are being named on the separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max)					
New Polyether Based Monomers and Highly Cross-linked Amphiphile Resins					
CORRESPONDENCE ADDRESS					
Direct all correspondence to:					
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ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification Number of Pages		37		<input type="checkbox"/> CD(s), Number	
<input checked="" type="checkbox"/> Drawing(s) Number of Sheets		—		<input type="checkbox"/> Other (specify)	
<input type="checkbox"/> Application Data Sheet, See 37 CFR 1.76					
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27				FILING FEE AMOUNT (\$)	
<input checked="" type="checkbox"/> A check or money order is enclosed to cover the filing fee				\$160.00	
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<input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached					
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
<input checked="" type="checkbox"/> No.					
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are:					

Respectfully submitted,

SIGNATURE

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Date

July 31, 2003

REGISTRATION NO.
If appropriate)

24,990

Docket Number:

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14.

[SOR.PAT.FORM 110 - 02/2001]

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08/04/03

**NEW POLYETHER BASED MONOMERS AND HIGHLY CROSS-
LINKED AMPHIPHILE RESINS**

TECHNICAL FIELD

[0001] This invention relates to a polymeric support for use in peptide synthesis, and in the field of bioorganic and organic chemistry. The invention also relates to a method of preparation thereof as well as to intermediates which can be used in such preparation. More particularly, the invention relates to a PEG, PPG and/or poly (THF) based polymer which can be used in the form of solid support in solid and liquid phase synthesis, chromatography, for scavenging purposes and immobilization of proteins and reagents.

BACKGROUND ART

[0002] The search for more stable amphiphilic resins is nowadays needed. Most of the presently known resins of this kind are based on polystyrene-PEG, polyamide, polyester or any kind of polymerized vinylic core. Their main drawback is their low chemical stability. CLEAR® (Kempe *et al.*, (1996), J. Am. Chem. Soc., 118, 7083-7093 and (1999), US Pat. 5,910,554) and PEGA® (Meldal, (1992), Tetrahedron Lett., 33, 3077-3080 and (1993), WO 93/16118) resins are cleaved in nucleophilic conditions (e.g. hydrolytic) as TentaGel® (Bayer, (1990), US Pat. 4,908,405 and (1991), Angew. Chem. Int. Ed. Engl. 30, 113-129) in acidic media.

[0003] Resins based on primary ether bound can be used to solve some problems, however other problems remain. The presence of the polystyrene core limits the ability of the final resin to perform for example the standard Friedel-Crafts reaction and generally have low loading capacity (e.g. between 0.2 and 0.5mmol/g to ArgoGel®) (Labadie *et al.*, (1997), WO 97/27226 and Gooding *et*

al., (1999), J. Comb. Chem., 1, 113-123). Reaching higher loadings lowers the final amphiphilicity of the resin because the PEG content is decreasing proportionally (e.g. Rapp Polymere's HypoGel®).

[0004] Few examples of non-polystyrene-PEG based resins are known. Meldal showed the usefulness of the POEPOP resin (Renil *et al.*, (1996), Tetrahedron Lett., 37, 6185-6188) based on PEG epoxide, and the SPOCC (Rademann *et al.*, (1999), J. Am. Chem. Soc., 121, 5459-5466 and Meldal *et al.*, (2000), WO 00/18823) based on PEG oxetane. Unfortunately, the use of non-conventional polymerization conditions with silicone oil and an appropriate surfactant gives a high cost manufacturing process (Grøtli *et al.*, (2001), J. Comb. Chem., 3, 28-33). Furthermore, low loadings are obtained when higher cross-linker (CL) content is used to give better mechanical stability. EXPO₃₀₀₀ (Tornøe *et al.*, (2002), Tetrahedron Lett., 43, 6409-6411) is a derivative of the former SPOCC resin based on PEG dioxetane with a silylated CL that gives a high amphiphilic resin employed in synthesis and enzymatic assays.

[0005] Recently, Oishi (Miwa *et al.*, (2001), Polymer Journal, Vol.33, No.12, 927-933) showed the use of a similar oxetane based on POE as a new polymer electrolyte for lithium batteries. The polymerization process is induced by LiBF₄ (or LiPF₆ as further electrolyte). The final polymer is nevertheless not in a beaded form and not employed for any organic chemistry reaction. The difference between the Meldal's monomers (used for the SPOCC synthesis) and the ones presented in Oishi's article is the nature of the methyl group replaced by a ethyl one.

[0006] Côté (Côté, (2002), WO 02/40559) covered many types of resins by generating resins based on PEG and/or PPG. The main idea behind this reference is the use of a highly cross-linked polyacrylate resin that is reduced to a polyol resin and then reacts with ethylene oxide under basic conditions to give a high amphiphilic polymer with from low to moderate loadings (e.g. 0-0.9 mmol/g). The great advantage of this resin is the simplicity of the polymerization

step (normal suspension) compared to the SPOCC. The drawback is a low mechanical stability of the final resin. The stickiness of the final polymer gives problems of manipulation. This characteristic is confirmed with similar polymers based on polyacrylate chemistry by the work of Fréchet (Kita *et al.*, (2001), J. Comb. Chem., 3, 564-571), and Tuncel (Tuncel, (2000), Colloid Polym. Sci., 278, 1126-1138).

[0007] The use of divinylether as CL gives secondary ethers that are more susceptible to hydrolysis such as the Meldal's POEPOP. Finally, PEG diallylethers (known to give low molecular weight polymers) would give low mechanical stability polymers containing only primary ethers. The PEG vinyl ketone (that will be later reduced) offers an interesting alternative to polyether with primary ether having the right specifications.

[0008] As a general statement, the presence of PEG, PPG and/or poly (THF) in the polymer requires very high CL content to obtain waxy-solid and/or "friendly user" resin but the loading decreases as much. No PEG, PPG and/or poly (THF) based polymer have been reported to be amphiphilic, high-loaded and non-sticky.

[0009] Dörwald (Dörwald, (2000), Organic Synthesis on Solid Phase, Chap. 2. Wiley-VCH Verlag, Weinheim, Federal Republic of Germany), Meldal (Meldal, (1997), Methods in enzymology, 289, 83-104, Academic Press, N.Y.) and Côté (Côté, (2002), WO 02/40559) offer more exhaustive reviews on amphiphilic resins.

[0010] The following specifications are required for a new and low-cost amphiphilic resin:

PEG based;

Primary ethers only (chemical stability);

High loadings available;

Solid to waxy state (non-sticky);

Mechanical stability;

Normal suspension polymerization (in water);

Low manufacturing cost (commercial products).

[0011] PEG macromonomers had been investigated in the early 90' until today by several groups. Ito (Chao *et al.*, (1991), Polym. J., Vol.23, 1045-1052) reported the synthesis and the polymerization behavior of several styrenic and standard methacrylic PEG monomers covering most of the amphiphilic resins found today.

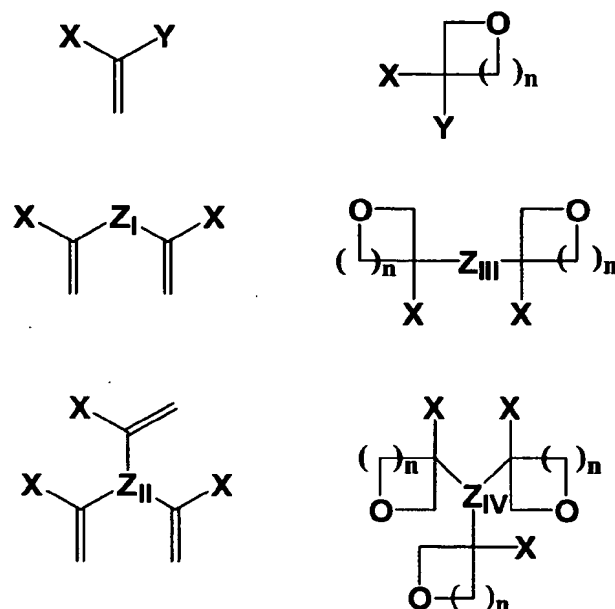
[0012] Yamada (Yamada *et al.*, (1991), Makromol. Chem., 192, 2713-2722; and (1993), J. Polym. Sci. Part A: Polym. Chem., Vol.31, 3433-3438) took another approach: the (a-PEG-methyl) acrylates. New amphiphilic monomers were synthesized and studied in copolymerization with methyl methacrylate and styrene. Unfortunately, very short methoxy-PEG chains of 1 to 3 EO were used, thus limiting the real amphiphilic potential of the final polymer. Moreover, only soluble linear polymers were reported and furthermore without any commercial uses.

[0013] Mathias reported new types of CL based on (a-Y-methyl) acrylates (where Y = malonitrile) (Tsuda, T. *et al.*, (1993), Macromol., Vol.26, 6359-6363); and tetraethylene glycol di(a-fluoroalkoxy-methyl) acrylate (Jariwala, C.P. *et al.*, (1993), Macromol. Vol.26, 5129-5136). Moreover, Mathias showed how these short CL have the tendency to cyclopolymerize instead of "really" cross-link.

[0014] Maillard (Philippon *et al.*, (1997) brings new approaches to synthesize macrocycles (mainly crown ethers). By the use of short PEG-acrylate and (a-PEG-methyl) acrylate (3 EO units only) that are submitted to radical reductive conditions (with Bu_3SnH), several crown ethers were obtained.

[0015] Finally, no example of monomers, CL and beaded insoluble polymers based on (α -PEG-methyl) acrylates has been published (review of Yamada *et al.*, (1994), Progr. Polym. Sci., Vol.19, 1089-1131).

[0016] It is an object of the present invention to provide a simple monomer design to give maximum loading on the final polymerized material versus known monomers and CL. Usual solid supports are synthesized by the mean of monomers and CL that contain:



Where:

X = H and/or CH_3 ;

Y = EWG (electron withdrawing group) and/or aryls with anything linked to it;

Z, Z_{III} and Z_{IV} = anything;

Z_I = EWG – spacer – EWG;

Z_{II} = (EWG) $_2$ – spacer – EWG;

n = 0 or 1.

[0017] It is an object of the present invention to provide the use of high percentage of CL without affecting the final loading of the resulting polymer contrary to what is presently found in the literature. As mentioned above, amphiphilic resins are using standard acrylates, methacrylates, acrylamides and/or methacrylamides where high CL content is needed to obtain a non-sticky polymer. This problem occurs also in the case of epoxide and/or oxetane based polymers.

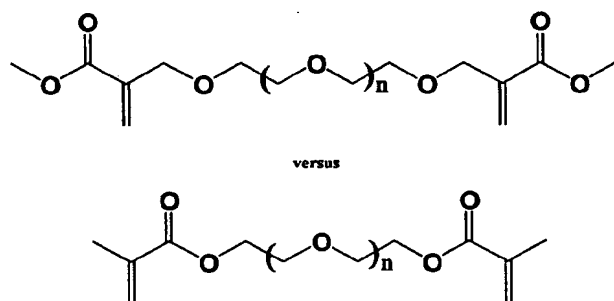
[0018] It is an object of the present invention to allow the parameter X to be anything but H and/or CH_3 . This way, it is possible to obtain high functionalized monomers and CL, therefore polymers. In the monomer area, it gives the possibility of a double functionalized monomer and in the CL area, it is possible to get a chemical function at each end of it where X can be used further as an handle, linker and/or spacer for SPPS (solid phase peptide synthesis) and SPOS (solid phase organic synthesis) where standard CL don't give so. This feature offers the opportunity of getting high CL polymers with 2 usable chemical functions (CF) (or more) at each ends of the CL on the polymer's core. This is not found anywhere else in the literature for uses as solid support. Indeed, all of the reported polymeric solid supports are based on monomers and/or CL where $\text{X} = \text{H}$, CH_2 and/or CH_2CH_3 . Bifunctional monomers and/or CL are known (e.g. fumaric, maleic and itaconic acid based) but each is susceptible to hydrolysis and/or nucleophilic attack. Divinylbenzene is also a bifunctional CL but no CF is still available once polymerized.

[0019] It is an object of the present invention to show the effect or retrieving the standard EWG in Z_I and Z_{II} . Indeed, replacing X by a EWG (and/or ERG (electron-releasing group) and/or any aryl) and Z_I and Z_{II} by a non hydrolysable CF, one obtains a stable CL that gives therefore a stable polymer with 2 CF that can be used further as handle, linker and/or spacer for SPPS and SPOS. In the case of epoxides and/or oxetanes, this effect is non observable but replacing X by a EWG and/or ERG (electron-releasing group) and/or anything

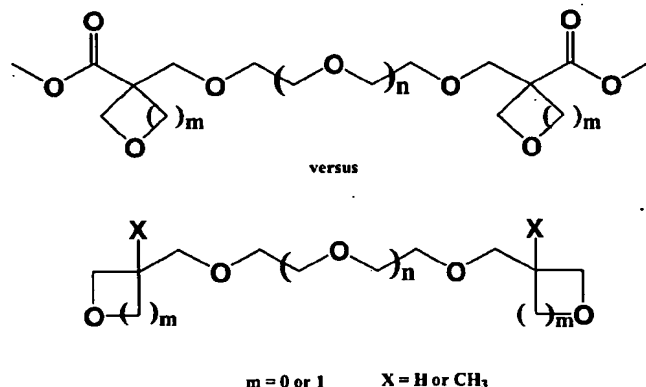
(but H and/or CH₃ and/or pure alkane), we obtain “well-functionnalized” monomers and CL overcoming the drawback of such materials.

[0020] It is an object of the present invention to provide highly functionalized non hydrolysable CL (the obtained polymer contains primary ether) wherein (as a non-limiting example) differences between those of the present invention and the standard PEG CL, include:

[0021] *Acrylic CL derivative*: normal suspension polymerization process in water is possible.

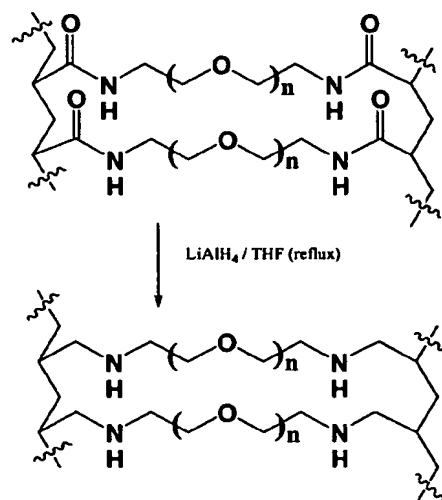


[0022] *Epoxide and/or oxetane CL derivatives*: non-aqueous normal and/or inverse suspension polymerization processes are possible for epoxides and/or oxetanes (see POEPOP (Renil *et al.* (1996)) and SPOCC (Rademann *et al.*, (1999)) polymerization processes).



[0023] It is another object of the present invention to provide a process for polymerizing standard PEG-PPG and/or poly(THF) (meth)acrylamide monomers and/or CL, and reduce the final polymer to obtain a polyamine resin where

secondary and/or tertiary amine can later be used as linker for SPPS and/or SPOS (Meldal, M., (1992), *Tetrahedron Lett.*, 33, 3077-3080). As a non-limiting example:



[0024] It is another object of the present invention to provide a new family of polymeric solid supports based on a PEG, PPG or poly (THF) matrix.

[0025] It is another object of the present invention to provide a method for the synthesis of such polymeric solid supports.

[0026] It is an object of the present invention to provide a new family of monomers and CL based on a PEG, PPG or poly (THF) matrix.

[0027] It is an object of the present invention to provide a new family of (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) monomers where X = oxygen, sulfur, PEG, PPG and/or poly (THF).

[0028] It is another object of the present invention to provide a polymeric matrix based on the copolymerization of a PEG, PPG and/or poly (THF) secondary, tertiary, comb-like, star-shaped CL having:

(a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) monomers (e.g. acrylates, acrylamides, acrylonitriles, acroleins, vinyl ketones (Iseri *et al.*, (2000), *J. Appl.*

Polym. Sci., 77, 509-516), vinyl halogens and styrenes based) where X = oxygen, sulfur, PEG, PPG and/or poly (THF)), divinylbenzene and/or any polymerizable monomer.

[0029] Acrylamide and/or methacrylamide end-groups (that will be later reduced once polymerized to an amine).

[0030] It is another object of the present invention to provide a new type of monomer based on the use of (a-halomethyl) vinyl-EWG (such as 2,3-dichloropropene or 2,3-dibromopropene) with oxygen, sulphur, PEG, PPG and/or poly (THF).

[0031] It is another object of the present invention to provide methodologies toward the synthesis of (a-alkoxy and/or hydroxymethyl) vinyl-EWG (and/or ERG and/or aryl) derivatives (for example: the Baylis-Hillman reaction (Yu *et al.*, (2001), J. Org. Chem. Vol.66, 5413-5418 and citations therein)). The resulting products can be derivatized in the aforementioned monomers and/or CL. The resulting hydroxyl groups can further be derivatized in other CF and/or linkers found in SPPS and/or SPOS. The hydroxyl group can be reduced to alkane giving the standard (a-alkoxymethyl) vinyl-EWG (and/or ERG and/or aryl) derivatives. More vigorous Baylis-Hillman conditions (Challenger *et al.*, (1999), Tetrahedron Lett., 40, 2187-2190) give the opportunity of using simple products such as alcohol, *t*-butyl acrylate, paraformaldehyde and a catalyst, to give directly the aforementioned monomers and/or CL. Another method for the synthesis of (a-alkoxymethyl) acrylates has been developed by a group of Guilford Pharmaceuticals by the use of the carboxylic acid derivative and Meldrum's acid. Mathias (Colletti *et al.*, 1991) reported the synthesis of such monomers by the dehydration of a (a-hydroxymethyl) acrylate in absolute ethanol with sulfuric acid. All of these methods of synthesizing (a-alkoxymethyl) vinyl-EWG derivatives are included in the present invention.

[0032] It is another object of the present invention to provide a new type of monomer based on the use of epoxides and/or oxetane groups with a a-EWG

(such as ester, nitrile, amide, aldehyde, ketone, halogens, nitro, sulfoxide) and/or any other CF (except H and CH₃) especially aryls with PEG, PPG and/or poly (THF). These groups could be later derivatized in other CF and/or linkers found in SPPS and/or SPOS before and/or after polymerization. It is another object of the present invention to provide a new type of polymer based on the aforementioned (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivative (where X = oxygen, sulfur, PEG, PPG and/or poly (THF)) as monomer and/or CL copolymerized with or without styrene and/or divinylbenzene and/or any polymerizable monomer.

[0033] It is another object of the present invention to provide a new type of polymer based on the aforementioned PEG, PPG and/or poly (THF) acrylamide and/or methacrylamide as monomer and/or CL copolymerized with or without styrene and/or divinylbenzene and/or any polymerizable monomer that will later be reduced to a polyamine.

[0034] It is another object of the present invention to provide a new type of monomers and/or CL based on the aforementioned (a,a'-X-Y-epoxide and/or oxetane) where X = oxygen, sulfur, PEG, PPG and/or poly (THF)) and Y = anything (but H, CH₃ and CH₂CH₃) as monomer and/or CL that can be mono and/or polysubstituted by such cyclic ethers alone or in admixture. The resulting monomers and/or CL could be polymerized in the same manner as Meldal's monomers used for the synthesis of POEPOP and SPOCC. The addition of a-EWG and/or any other CF (except H, CH₃ and CH₂CH₃) to an epoxide and an oxetane fulfill the drawback of low substitution resins resulting from original work based on PEG-epoxide and oxetane.

[0035] It is another object of the present invention to provide a new type of polymer based on the aforementioned (a,a'-X-Y-epoxide and/or oxetane) where X = oxygen, sulfur, PEG, PPG and/or poly (THF)) and Y = anything (but H, CH₃ and CH₂CH₃) as monomer and/or CL copolymerized with or without any polymerizable monomer.

[0036] It is another object of the present invention to provide polymeric solid supports that can be used for the solid phase synthesis of peptides, oligonucleotides, oligosaccharides and in combinational and traditional organic chemistry.

[0037] It is another object of the present invention to provide resins that can be used in liquid phase synthesis, chromatography, for scavenging purposes, and for protein and reagents immobilisation.

[0038] It is another object of the present invention to provide a method for the synthesis of such monomers and CL.

[0039] It is another object of the present invention to provide a method of O-alkylation by phase transfer catalysis (PTC) for the synthesis of such monomers and CL.

[0040] It is another object of the present invention to provide a method of O-alkylation by the Baylis-Hillman reaction (and its derivatives) for the synthesis of such monomers and CL.

DISCLOSURE OF INVENTION

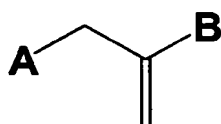
[0041] As mentioned above, the standard monomers and CL are based on acrylic and/or methacrylic esters and/or amides and/or epoxides and/or oxetanes. The present invention relates to a CL polyether which is obtained by:

copolymerization of a monomer comprising at least a) one (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivatives where X= oxygen, sulphur, PEG, PPG and/or poly (THF)) and/or b) styrene and/or c) any polymerizable monomer with d) a PEG, PPG and/or poly (THF) CL having at least one (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivative where X = oxygen, sulfur, PEG, PPG and/or poly (THF)) and/or e) a PEG, PPG, poly (THF) and/or any CL having at least an acrylamide (and/or methacrylamide) end group (that will later

be reduced once polymerized to a polyamine) f) divinylbenzene (except the pure styrene-divinylbenzene mixture) with variations from 0.1 to 100% in CL content; or by:

copolymerization of a monomer comprising at least a) one (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen, sulphur, PEG, PPG and/or poly (THF)) and Y = anything (but H, CH₃ and CH₂CH₃) and/or b) any polymerizable monomer containing an epoxide and/or oxetane moiety with c) a PEG, PPG and/or poly (THF) CL having at least one (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen, sulphur, PEG, PPG and/or poly (THF)) and Y = anything (but H, CH₃ and CH₂CH₃) with variations from 0.1 to 100% in CL content.

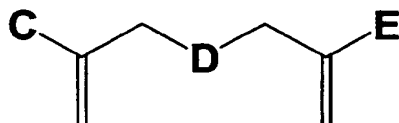
[0042] In accordance with a preferred embodiment, the monomer in 1) is a polymerizable compound having the general formula



wherein

A represents H, alkyl, aryl, aralkyl, PEG, PPG, poly (THF), alcohol, amine, aldehyde and/or halogen derivatives thereof; **B** represents EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and any other CF (except H and CH₃) especially aryls.

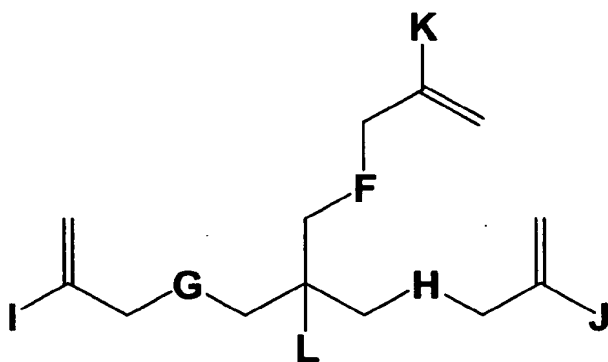
[0043] The CL in 1) preferably comprises a PEG, PPG or poly (THF) based polymer. For example, it may be a secondary cross-linker of the general formula



wherein

D represents alkyl, aryl, aralkyl, oxygen, sulfur, PEG, PPG and/or poly (THF) derivatives thereof; **C** and **E** represent independently EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and any other CF (except H and CH₃) (especially aryls) and/or a PEG, PPG and/or poly (THF) and/or any secondary CL having at least an acrylamide (and/or methacrylamide) end group (that will be lately reduced once polymerized to polyamine).

[0044] In 1), it may also be a tertiary CL of the general formula



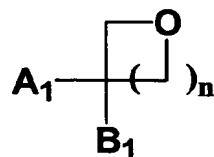
wherein

F, **G** and **H** represent independently alkyl, aryl, aralkyl, oxygen, sulfur, PEG, PPG and/or poly(THF) derivatives thereof; **I**, **J** and **K** each represent independently an EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and any other CF (except H and CH₃) (especially aryls) and/or a PEG, PPG and/or poly (THF) and/or any tertiary CL having at least an acrylamide (and/or methacrylamide) end group (that will be lately reduced once polymerized to polyamine). **L** represents H, alkyl, aryl, aralkyl, glycidyl or an alcohol protecting group, or a PEG, PPG and/or poly (THF) and/or any CF having at least one acrylamide (and/or methacrylamide) end group (that will be later reduced once polymerized to polyamine).

[0045] Comb-like (Ito *et al.*, (1992), Macromol. Vol.25, 1534-1538) and star-shaped CL are also covered by the present invention. Theses CL are functionalized with PEG, PPG and/or poly (THF) with the aforementioned (a-

methyl) vinyl-EWG and/or a,a'-X-Y-(epoxide and/or oxetane) and/or derivatives and/or having at least one acrylamide (and/or methacrylamide) end group (that will later be reduced once polymerized to a polyamine) at the end of each "tentacles".

[0046] In accordance with a preferred embodiment, the monomer in 2) is a polymerizable compound having the general formula

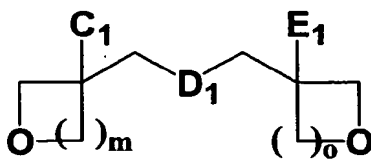


wherein

A_1 represents H, alkyl, aryl, aralkyl, PEG, PPG, poly (THF), alcohol, amine, aldehyde and/or halogen derivatives thereof; B_1 represents EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and anything (but H and CH_3).

$n = 0$ or 1.

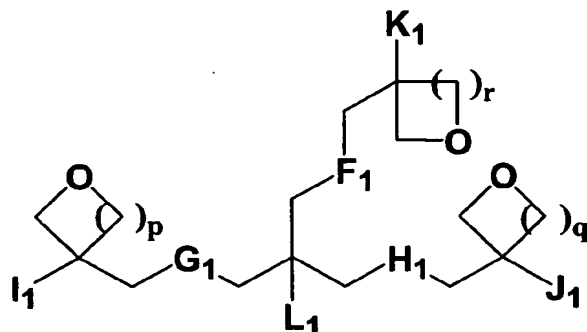
[0047] The cross-linker in 2) preferably comprises a PEG, PPG or poly (THF) based polymer. For example, it may be a secondary CL of the general formula



wherein

D_1 represents alkyl, aryl, aralkyl, oxygen, sulphur, PEG, PPG and/or poly (THF) derivatives thereof; C_1 and E_1 represent independently EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and anything (but H, CH_3 and CH_2CH_3) m and/or o are independently 0 or 1.

[0048] In 2), it may also be a tertiary CL of the general formula



wherein

F₁, G₁ and H₁ represent independently alkyl, aryl, aralkyl, oxygen, sulphur, PEG, PPG and/or poly(THF) derivatives thereof; I₁, J₁ and K₁ each represents independently an EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and anything (but H and CH₃); L₁ represents H, alkyl, aryl, aralkyl, glycidyl or an alcohol protecting group; p, q and r are independently 0 or 1.

[0049] In accordance with a preferred embodiment, the method in 1) according to the invention comprises (a) copolymerizing the above vinylic polymerizable compound with a compound selected from the above vinylic secondary, tertiary, comb-like, star-shaped and/or divinylbenzene CL to give the above polymer, (b) reacting the polymer to give a polyester (by transesterification or not), polyol, polyaldehyde, polycarboxylic acid, polythiol and/or polyamine (from acrylamide and/or methacrylamide or not) resin that will be later derivatized.

[0050] In accordance with a preferred embodiment, the method defined in 2) according to the invention comprises (a) copolymerizing the above epoxide and/or oxetane polymerizable compound with a compound selected from the above epoxide and/or oxetane secondary, tertiary, comb-like, star-shaped CL to give the above polymer, (b) reacting the polymer to give a polyester (by transesterification or not), polyol, polyaldehyde, polycarboxylic acid, polythiol

and/or polyamine (from acrylamide and/or methacrylamide or not) resin that will be later derivatized.

[0051] According to the present invention, any of the new monomers and CL ester bond can be reacted to functionality useful for anchoring linkers used in SPPS and SPOS. The end groups of the monomers and/or CL may also contain alcohol, halogen, aldehyde, amino, carboxylic acid, thiol and/or phenyl groups that can be lately derivatized in (or with) useful linkers for peptide synthesis or bioorganic and organic chemistry.

[0052] Monomers and/or CL can be functionalized before or after the polymerization with different linkers useful for peptide, bioorganic and organic chemistry, and the like.

Examples of derivatization of the final polymer:

Chemical function	Reducing	Nucleophilic	Hydrolytic
Ester	Alcohol or aldehyde	Alcohol, ester and amide	Carboxylic acid
Amide	Amine	Alcohol	Carboxylic acid
Nitrile	Amine	Alcohol	Carboxylic acid
Aldehyde	Alcohol	Alcohol	-----
Ketone	Alcohol	Alcohol	-----
Nitro	Amine	-----	-----
Sulfoxide	Thiol	-----	-----
Sulfonate	Thiol	-----	-----

[0053] The cross-linked polymer according to the invention is designed in such a way that it is possible to modify its properties by an appropriate choice of

monomers (including single monomer, secondary, tertiary, comb-like and/or star-shaped CL). Indeed, the length of each monomer and/or CL will affect the swelling of the final resin. That way, it is possible to obtain a resin with several mechanical and swelling behaviours. That feature is greatly helpful for the design of resins for continuous flow to batchwise synthesis. By using a longer monomer and/or CL, the polymer is a more porous polymer enabling high molecular weight molecule penetration, which is effective for peptide, oligonucleotide, oligosaccharide synthesis and protein immobilisation. Shorter monomers give a resin adapted for small molecule synthesis as found in current organic chemistry.

[0054] Furthermore, that physical aspect can be used for permeation chromatography where a porous matrix is essential. A harder resin will be useful for low to high pressure chromatography where a very small to no change in volume of the matrix is needed.

[0055] The chemical nature of the PEG, PPG and/or poly (THF) gives to the polymer an exceptional versatility in most of organic and aqueous solvents. In organic synthesis and chromatography, low to high polarity solvents are often used in the same experiment. The amphiphilic nature of the glycol derivatives according to the invention gives extraordinary swelling in solvents such as water, *N,N*-dimethylformamide, methanol, methylene chloride, tetrahydrofuran, acetone, toluene and chemical families associated therewith.

[0056] The cross-linked polymer in 1) is obtained by suspension radical copolymerization of a mixture (or not) of the aforementioned acrylic, acrylonitriles, acrylamides, acroleins, vinyl ketones, vinyl chloride and/or bromide derivative monomers (and/or styrene) with the aforementioned secondary, tertiary, comb-like and/or star-shaped CL and/or divinylbenzene.

[0057] The cross-linked polymer in 2) is obtained by suspension cationic copolymerization of a mixture (or not) of the aforementioned epoxides and/or oxetanes monomers with the aforementioned secondary, tertiary, comb-like

and/or star-shaped CL (for examples of such processes, see Renil *et al.*, (1996) and Rademann *et al.*, (1999)).

[0058] According to the invention, the functional groups L and L₁ can be modified chemically before or after the copolymerization, into several types of linkers such as alcohol, alkylalcohol, amino, alkylamino, aryl, alkyl, aralkyl, cyano, carboxyl, ester, mercapto, sulfo, sulfinio, sulfeno in any derivatives thereof or in any protected form. Furthermore, any already designed linker for organic, peptide, nucleotide and saccharide synthesis can be attached to the monomer (as L and/or L₁) or by any functionality described above as a spacer.

[0059] These linkers can be used for organic, peptide, protein, nucleotide and saccharide synthesis. They can also be used also for the immobilisation of protein and reagents or for chromatographic and scavenging purposes. End-capped monomers (such as alkyl and aryl in place of L and/or L₁) can be used as chromatographic devices as reversed-phase packing. Other polar functionality for L and/or L₁ such as SO₃H and NH₂ can be used in ion exchange and normal phase chromatography.

[0060] According to the present invention, it is possible to use other polymerizable monomers (especially styrene in the copolymerization of 1)) leading to the polymer according to the present invention.

[0061] The polymer can be generated into a preferred beaded (spherical) form by processes such as normal and inverse suspension, emulsion, dispersion, seeded or precipitation polymerizations. Normal and/or inverse suspension polymerization is the preferred method for the production of beads according to the present invention.

[0062] Bulk and solution polymerization should normally be avoided because no beads are thus formed. Nevertheless, powders obtained directly or by grinding and sieving of the bulk polymer and/or any other solid form of polymer can be obtained by these two processes and can be employed as solid support in the applications listed above.

[0063] Radical initiated polymerisation is the standard way by which vinyl monomers are polymerized although other methods can be used according to the present invention.

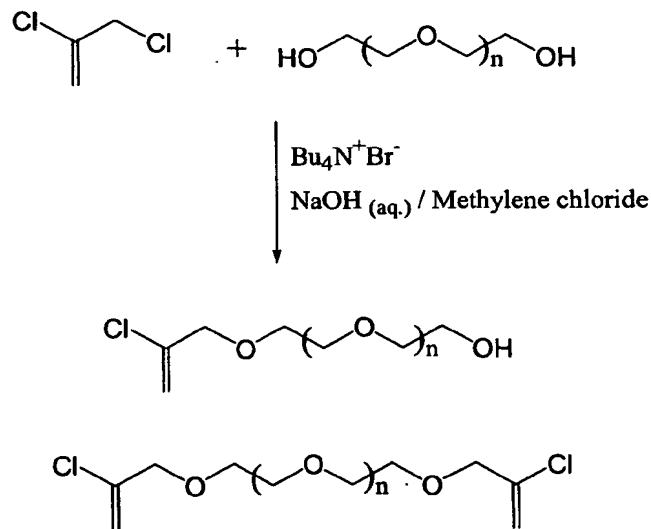
[0064] According to the present invention, the aforementioned “(α-methyl) vinyl-EWG” and/or acrylamide and/or methacrylamide monomers and/or CL may for example be copolymerized by radical polymerization with vinyl ether and allyl compounds that are known to copolymerize easily in the presence of other vinyl compounds such as acrylic, methacrylic acids and/or esters and/or derivatives.

[0065] The polymerization is normally initiated by products that upon heating, ultraviolet and/or gamma radiation give free radicals. In the present invention organic peroxides such as benzoyl and lauroyl peroxides are preferred. Heating the reaction mixture is the preferred way to form these free radicals.

[0066] In a same approach, vinyl and/or allyl ethers can be copolymerized with the aforementioned epoxides and/or oxetanes monomers and/or CL by cationic and/or anionic polymerization processes.

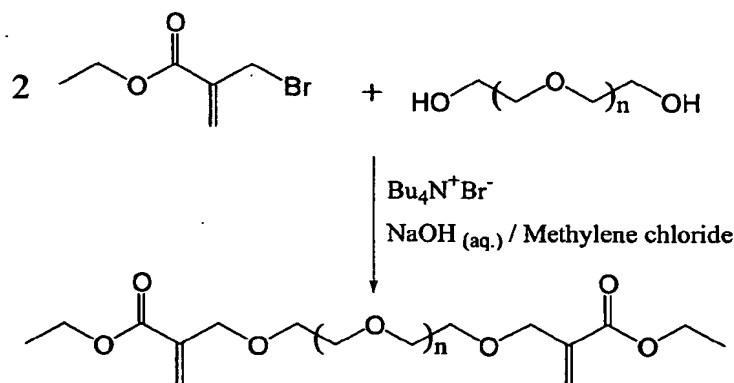
[0067] The invention will now be illustrated by means of the following non limiting examples.

Example 1: Synthesis of PEG400 bis ((α-methyl) vinyl chloride) under PTC conditions:



[0068] In a round bottom flask of 250mL, PEG 400 (24g; 60mmoles) is dissolved in 75mL of methylene chloride under mechanical agitation. A solution of sodium hydroxide 33% (150mL; 50g; 1250mmoles) with tetrabutylammonium bromide (TBAB) (19.34g; 60mmoles) is added to the organic phase. 2,3-dichloropropene (13.32g;120mmoles) is gently introduced to the biphasic mixture. After 48h of stirring at room temperature, the organic phase is extracted then dried with Na_2SO_4 . The purification step is accomplished by means of a silica gel pad (hexanes/acetone: 1/1). The solvent is evaporated to dryness under vacuum. The final product is then dried under vacuum at 40°C overnight. Yield: 26.78g. The NMR spectrum shows a ratio between the vinylic protons and the PEG's methylene protons of 50% of mono and bis functionalized PEG 400.

Example 2: Synthesis of PEG3350 bis (ethyl (α-methyl)acrylate) under PTC conditions:

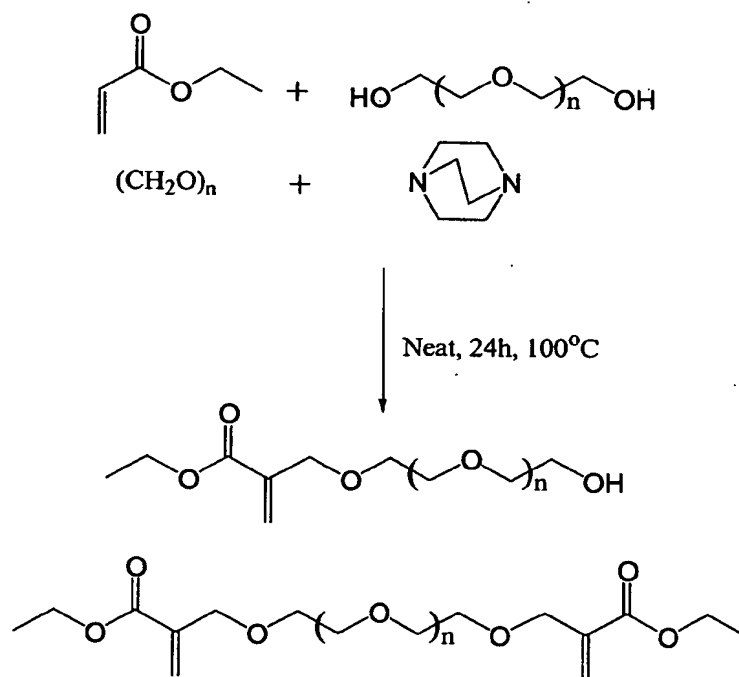


[0069] In a round bottom flask of 1L, PEG 3350 (35.5g; 10mmoles) are dissolved in 200mL of methylene chloride under mechanical agitation. A solution of sodium hydroxide 33% (200mL; 67.5g; 1675mmoles) with tetrabutylammonium bromide (TBAB) (0.645g; 2mmoles) is added to the organic phase. Ethyl (bromomethyl) acrylate (7.72g; 40mmoles) is gently introduced to the biphasic mixture. After 24-48h of stirring at room temperature, the organic

phase is extracted then dried with Na_2SO_4 . The solvent is evaporated under vacuum to dryness.

[0070] In a round bottom flask of 1L, under high-speed mechanical agitation, cold diethyl ether (300mL) is added to the insoluble product and then settled to remove ether by suction. This purification step is repeated three times. The final product is then dried under vacuum at 40°C overnight. Yield: 32.55g (92%) The NMR spectrum shows the right ratio between the vinylic protons and the PEG's methylene protons.

Example 3: Synthesis of PEG1500 mono & bis (ethyl (α -methyl)acrylate) under Baylis-Hillman conditions:

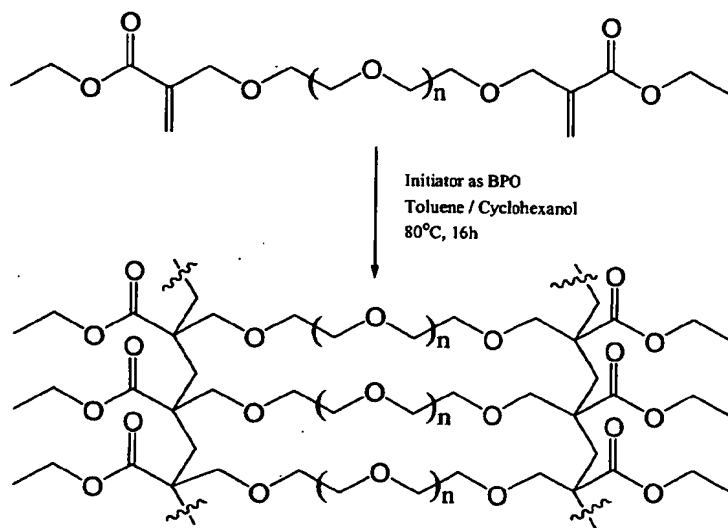


[0071] In a round bottom flask of 100mL, PEG 1500 (15,0g; 10mmoles) and DABCO (3,96g; 35mmoles) are dissolved in ethyl acrylate (25mL; 23,1g; 230mmoles) under mechanical agitation. At 100°C , paraformaldehyde (3,6g; 120mmoles) is added to the organic phase in several portions during 2 hours. After 24h of stirring at 100°C , the organic phase is cooled to the room

temperature. The flask's content is dissolved in 200mL of acetone. Insoluble matter is filtered and the solvent is evaporated under vacuum to dryness.

[0072] The crude product is dissolved with a minimum of methylene chloride (circa 10-20mL) in a round bottom flask of 500mL. Under high-speed mechanical agitation, MTBE (300mL) is added to precipitate the product(s). After 2 hours at 4°C, the precipitate is filtered (MTBE solution is containing impurities) and washed with more MTBE (2x50mL) and finally with hexanes (3x50mL). This purification step is repeated twice. The final product is then dried under vacuum at 40°C overnight. Yield: 14,19g (82%) The NMR spectrum shows the presence of a mixture of 50% of PEG1500 mono & bis (ethyl (α-methyl)acrylate).

Example 4: Synthesis of poly(di(ethyl (PEG3350methyl)ester)):



Monomer phase:

Di(ethyl (PEG3350methyl)acrylate) (27.5 g; 7,75 mmol)

27.5mL of cyclohexanol

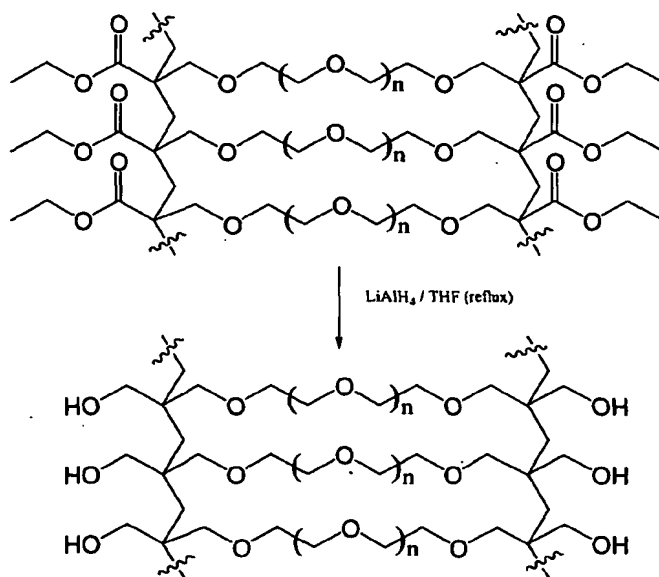
27.5mL of toluene

BPO 75% (Benzoyl peroxide) (1.65g ; 4.6 mmol)

[0073] In a 500 mL tri neck flask, under nitrogen, $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ (48g; 195mmoles) and 25mg of sodium dodecylbenzenesulfonate are dissolved in 250 mL of distilled water at 300 r.p.m. at 25°C. A solution of NaOH (15.5g; 390mmoles) in 50mL of distilled water is added slowly to the previous aqueous solution to form the final suspension of $\text{Mg}(\text{OH})_2$ media.

[0074] In a separate 125 mL Erlenmeyer flask, the monomer phase is prepared by mixing the monomer, porogens (Kita *et al.*, 2001) and initiator. The monomer phase is then poured into the aqueous phase containing the suspending agents and equilibrates for 30 minutes. The polymerization is realized by heating the suspension during 16h at 80°C. The suspension is cooled and treated with HCl 4N (125mL; 500mmoles) then filtered on a Büchner funnel. The resin is then washed with hot distilled water (4x1 L), acetone (2x250 mL), methanol (2x250 mL) and diethyl ether (2x100 mL). The resin is dried at 40°C under vacuum overnight. Obtained weight: 25.06g. Yield: 91%.

Example 5: Reduction of the polymethacrylate from example 3 to the polyol resin



[0075] In a 1L round bottom flask, under dry nitrogen, the polymethacrylate resin from example 3 was swelled in 500mL of THF with vigorous mechanical agitation. LiAlH_4 (2g; 52.7mmoles) was added carefully. After refluxing during 16 h, the suspension is cooled and methanol (100mL) is slowly added and 50 mL of HCl 4N to quench the reaction. The final mixture is filtered on a Büchner funnel. The resin is rinsed with HCl 12N, distilled water, methanol acetone and diethyl ether (2 x 250mL each). The resin is dried at 40°C under vacuum overnight. The IR spectrum shows the disappearance of the ester (at 1734cm^{-1}) to give strong absorbance of the OH at 3550cm^{-1} . The loading of the final resin is 0.45mmol/g (by nitrogen elemental analysis), based on the phenyl carbamate derivative* (Lee *et al.*, (1995) US Pat. 5,466,758 and Park *et al.*, (1997), Tetrahedron Lett., 38, 591-594).

[0076] From the reaction of phenyl isocyanate (5 equivalents of the expected value) with the polyol in methylene chloride during 16hours.

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CLAIMS

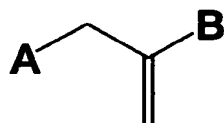
1. A cross-linked polyether which is obtained by:

1) copolymerization of a monomer comprising at least a) one (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivatives where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and/or b) styrene and/or c) any polymerizable monomer with d) a PEG, PPG and/or poly (THF) CL having at least one (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivative where X = oxygen, sulfur, PEG, PPG and/or poly (THF)) and/or e) a PEG, PPG, poly (THF) and/or any CL having at least an acrylamide (and/or methacrylamide) end group (that will later be reduced once polymerized to a polyamine) f) divinylbenzene (except the pure styrene-divinylbenzene mixture) with variations from 0.1 to 100% in CL content;

or by:

2) copolymerization of a monomer comprising at least a) one (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and Y = anything (but H, CH₃ and CH₂CH₃) and/or b) any polymerizable monomer containing an epoxide and/or oxetane moiety with c) a PEG, PPG and/or poly (THF) CL having at least one (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and Y = anything (except H, CH₃ and CH₂CH₃) with variations from 0.1 to 100% in CL content.

2. Cross-linked polyether according to claim 1, wherein said monomer in 1) is a polymerizable compound having the general formula



wherein

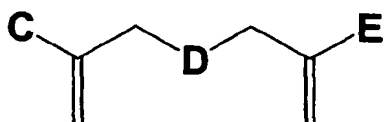
A represents H, alkyl, aryl, aralkyl, PEG, PPG, poly (THF), alcohol, amine, aldehyde, thiol, and/or halogen derivatives thereof;

B represents EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and/or ERG and/or aryl.

3. Cross-linked polyether according to claim 1, wherein said monomer in 1) is styrene.

4. Cross-linked polyether according to claim 1, wherein said polymer in 1) and 2) comprises a PEG, PPG and/or poly (THF) based CL.

5. Cross-linked polyether according to claim 4, said CL in 1) is a secondary CL of the general formula



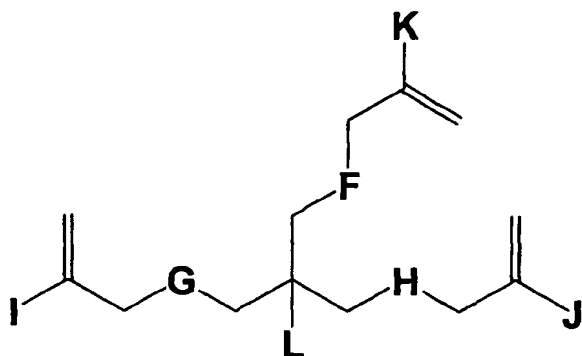
wherein

D represents alkyl, aryl, aralkyl, oxygen, sulphur, PEG, PPG and/or poly (THF) derivatives;

C and **E** represent independently EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and/or ERG and/or aryl.

6. Cross-linked polyether according to claim 4, wherein said secondary CL in 1) is a PEG, PPG and/or poly (THF) and/or any secondary CL having at least an acrylamide (and/or methacrylamide) end group (that will be later reduced once polymerized to polyamine).

7. Cross-linked polyether according to claim 4, wherein said CL is a tertiary CL in 1) of the general formula



wherein

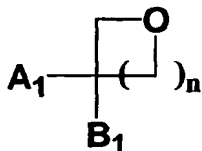
F, G and H represent independently alkyl, aryl, aralkyl, oxygen, sulfur, PEG, PPG and/or poly (THF) derivatives;

I, J and K represent independently EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and/or ERG and/or aryl.

L represents H, alkyl, aryl, aralkyl, glycidyl or an alcohol protecting group.

8. Cross-linked polyether according to claim 4, wherein said CL is a comb-like and/or star-shaped CL derivatized with a (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivatives (such as acrylates, acrylamides, acrylonitriles, acroleins, vinyl ketones, vinyl chlorides and/or bromides, styrenes) where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and/or any aforementioned CL having at least an acrylamide (and/or methacrylamide) end group (that will be later reduced once polymerized to polyamine).

9. Cross-linked polyether according to claim 1, wherein said monomer in 2) is a polymerizable compound having the general formula



wherein

A₁ represents H, alkyl, aryl, aralkyl, PEG, PPG, poly (THF), alcohol, amine, aldehyde and/or halogen derivatives thereof;

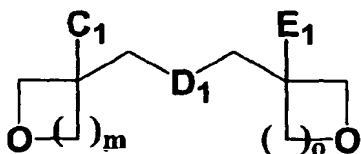
B₁ represents EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and anything (but H and CH₃).

n = 0 or 1.

10. Cross-linked polyether according to claim 1, wherein said monomer is styrene.

11. Cross-linked polyether according to claim 1, wherein said polymer comprises a PEG, PPG and/or poly (THF) based cross-linker.

12. Cross-linked polyether according to claim 4, said CL in 2) is a secondary CL of the general formula



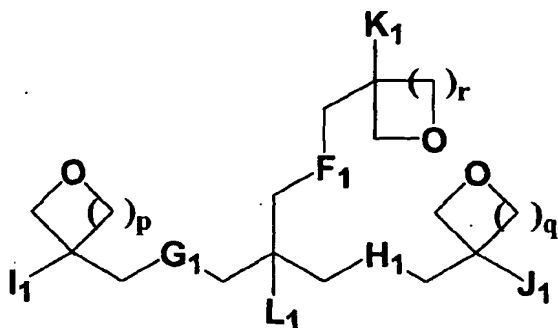
wherein

D₁ represents alkyl, aryl, aralkyl, oxygen, sulfur, PEG, PPG and/or poly (THF) derivatives thereof;

C₁ and **E₁** represent independently EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and anything (but H, CH₃ and CH₂CH₃)

m and/or **o** are independently 0 or 1.

13. Cross-linked polyether according to claim 4, wherein said CL in 2) is a tertiary CL of the general formula



wherein

F_1 , G_1 and H_1 represent independently alkyl, aryl, aralkyl, oxygen, sulfur, PEG, PPG and/or poly(THF) derivatives thereof;

I_1 , J_1 and K_1 each represents independently an EWG (such as halogen, formyl, cyano, ester, amide, ketone, nitro, sulfoxide, sulfonate and so on) and anything (but H and CH_3);

L_1 represents H, alkyl, aryl, aralkyl, glycidyl or an alcohol protecting group;

p , q and r are independently 0 or 1.

14. Cross-linked polyether according to claim 4, wherein said CL in 2) is a comb-like and/or star-shaped CL derivatized with a (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and Y = anything (but H and CH_3).

15. Cross-linked polyether according to claim 1, wherein said monomers in 1) from claims 2, 5, 7 and 8 can be produced by the Baylis-Hillman reaction (and its derivatives) and/or by acid catalysis from an alcohol and a vinyl-EWG (and/or ERG and/or aryl) derivative as described in claim 1 in a dehydration process.

16. Cross-linked polyether according to claim 4, wherein said CL in 1) is a PEG, PPG and/or poly (THF) CL having at least an acrylamide (and/or methacrylamide) end group (that will be lately reduced once polymerized to polyamine).

17. Cross-linked polyether according to claim 4, wherein said CL in 1) is divinylbenzene.

18. Cross-linked polyether according to claims 2, 4, 5, 7, 9, 12 and 13 wherein functional groups A, A₁, B, B₁, C, C₁, E, E₁, I, I₁, J, J₁, K, K₁ and L, L₁ are chemically modified to provide linkers for organic, peptide, protein, nucleotide and saccharide synthesis, for the immobilisation of proteins and reagents, for chromatographic and scavenging purposes, as reverse phase packing and chromatographic devices, in ion exchange and normal phase chromatography.

19. Cross-linked polyether according to claim 18, wherein said linkers are selected from alcohol, alkylalcohol, halogeno, amino, alkylamino, aryl, alkyl, aralkyl, cyano, carboxyl, ester, mercapto, sulfo, sulfino, sulfeno, and derivatives thereof.

20. A method for the preparation of a cross-linked polyether according to claim 1, which comprises:

1) copolymerization of a monomer comprising at least a) one (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivatives where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and/or b) styrene and/or c) any polymerizable monomer with d) a PEG, PPG and/or poly (THF) CL having at least one (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivative where X = oxygen, sulfur, PEG, PPG and/or poly (THF)) and/or e) a PEG, PPG, poly (THF) and/or any CL having at

least an acrylamide (and/or methacrylamide) end group (that will later be reduced once polymerized to a polyamine) f) divinylbenzene (except the pure styrene-divinylbenzene mixture) with variations from 0.1 to 100% in CL content;

or by:

2) copolymerization of a monomer comprising at least a) one (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and Y = anything (but H, CH₃ and CH₂CH₃) and/or b) any polymerizable monomer containing an epoxide and/or oxetane moiety with c) a PEG, PPG and/or poly (THF) CL having at least one (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and Y = anything (but H, CH₃ and CH₂CH₃) with variations from 0.1 to 100% in CL content.

21. Method according to claim 20 in 1), which comprises (a) copolymerizing a polymerizable compound according to claim 2 with a compound selected from the group of secondary CL as defined in claim 5 and 6, a tertiary CL as defined in claim 7 and 8, a comb-like and/or star-shaped CL as defined in claim 8 and 17 and/or divinylbenzene as defined in claim 18 to give said polyether, (b) reacting said polyether to give a polyether derivative as aldehyde, amine, ketone, halogen, carboxylic acid, thiol, amide and/or ester resin.

22. Method according to claim 20 in 2), which comprises (a) copolymerizing a polymerizable compound according to claim 9 with a compound selected from the group of secondary CL as defined in claim 12, a tertiary CL as defined in claim 13, a comb-like and/or star-shaped CL as defined in claim 14 to give said polyether, (b) reacting said polyether to give a polyether derivative as aldehyde, amine, ketone, halogen, carboxylic acid, thiol, amide and/or ester resin.

23. Method according to claim 21, wherein said cross-linked polyether is obtained by suspension radical polymerization.
24. Method according to claim 22, wherein said cross-linked polyether is obtained by suspension cationic polymerization.
25. Method according to claim 21, which comprises carrying said copolymerization in the presence of additional polymerizable monomers especially styrene, acrylates, acrylamides, acrylonitriles, acroleins (and their methacrylic derivatives), vinyl ketones, vinyl chlorides and/or bromides.
26. Method according to claim 22, which comprises carrying said copolymerization in the presence of additional polymerizable monomers especially other epoxides, oxetanes, vinyl and allyl ethers.
27. Method according to claim 21 and 22, which comprises synthesizing the cross-linked polyether into beaded form.
28. Method according to claim 21, which comprises functionalizing said monomer and/or CL ((a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivatives (such as acrylates, acrylamides, acrylonitriles, acroleins, vinyl ketones, vinyl chlorides and/or bromides and styrenes) where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) with groups capable of anchoring linkers.
29. Method according to claim 22, which comprises functionalizing said monomer and/or CL (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen,

sulfur, PEG, PPG and/or poly (THF)) and Y = anything (but H and CH₃) with groups capable of anchoring linkers.

30. Method according to claim 21, which comprises functionalizing said acrylamide (and/or methacrylamide) monomers and/or CL with groups capable of anchoring linkers.

31. Method according to claim 28 and 30, wherein said groups are selected from aldehyde, alcohol, halogen, ketone, amino, and/or phenyl groups which can be derivatized into said anchoring linkers.

32. Method according to claim 21 and 22, which comprises forming, said beads by normal and/or inverse suspension.

33. Monomers and cross-linkers (except styrene and divinylbenzene) as defined in any one of claims 1 to 32

ABSTRACT

The needs for hydrophilic conditions in peptide synthesis, bioorganic and organic chemistry on solid support is still growing. The provision of a new chemical matrix compatible with these conditions is then welcomed. The present invention fulfils desired specifications generally rarely encountered with existing solid supports such as highly amphiphile behaviour. The solid support described herein is a poly (ethylene or propylene) glycol and/or poly (THF) based polymer that can be useful in solid and liquid phase synthesis, chromatography, for scavenging purposes and immobilisation of proteins and reagents. More specifically, the solid support is a cross-linked polyether which is obtained by :

1) copolymerization of a monomer comprising at least a) one (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivatives where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and/or b) styrene and/or c) any polymerizable monomer with d) a PEG, PPG and/or poly (THF) CL having at least one (a-X-methyl) vinyl-EWG (and/or ERG and/or aryl) derivative where X = oxygen, sulfur, PEG, PPG and/or poly (THF)) and/or e) a PEG, PPG, poly (THF) and/or any CL having at least an acrylamide (and/or methacrylamide) end group (that will later be reduced once polymerized to a polyamine) f) divinylbenzene (except the pure styrene-divinylbenzene mixture) with variations from 0.1 to 100% in CL content; or by:

2) copolymerization of a monomer comprising at least a) one (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and Y = anything (but H and CH₃) and/or b) any polymerizable monomer containing an epoxide and/or oxetane moiety with c) a PEG, PPG and/or poly (THF) CL having at least one (a,a'-X-Y-epoxide and/or oxetane) where X= oxygen, sulfur, PEG, PPG and/or poly (THF)) and Y = anything (but H and CH₃) with variations from 0.1 to 100% in CL content.

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